

combination antibiotics for multidrug-resistant (MDR)–*Pseudomonas aeruginosa* infections are limited. **Methods:** This retrospective, case–control observational study was based on chart review of the patients managed at the University of Kentucky. **Results:** In total, 143 patients with MDRO *Pseudomonas aeruginosa* infections were identified and divided into 2 groups: 1 group received newer BLBI combinations with or without aminoglycosides or polymyxins, for at least 72 hours, and the control group received carbapenem containing combination antibiotics or other antibiotics. Baseline characteristics and patient outcomes are shown in Table 1. **Discussion:** The newer BLBI combinations group consisted of 60.8% MDR *Pseudomonas* bacteremia, whereas the control group had 68.4% of MDR *Pseudomonas* respiratory cultures. Overall, the use of newer BLBI combinations such as ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam was associated with lower rates of acute kidney injury (AKI), shorter LOS, and lower mortality rates compared to the control group, and these differences were statistically significant. Because the 2 populations of patient differed significantly based on the site of infection (sepsis vs pneumonia), the data were reanalyzed to evaluate the impact of therapy on the occurrence of AKI, LOS, and mortality based on the site of infection. Only those patients with sepsis who received the newer combination drugs had significantly better rates of AKI, lower LOS, and had lower rates of mortality. The 2 treatment arms were not statistically different when comparing patients with pneumonia. Additionally, the use of these new combination therapies did not make a difference regarding readmission rates or duration of bacteremia for the patients included in the study.

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Time Above All Else: Pharmacodynamic Analysis of B-Lactams in Critically Ill Patients

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Background: Despite the development of new β -lactam agents, gram-negative resistance continues to be an increasing concern in the healthcare setting. The understanding and optimizing antimicrobial pharmacokinetics and pharmacodynamics are essential to enhance activity of appropriate therapy, improve clinical outcomes, and reduce the development of resistance. **Methods:** A pharmacodynamic analysis was performed for 4 β -lactams (aztreonam, cefepime, piperacillin/tazobactam, and meropenem) and 14 dosage regimens as either intermittent bolus (IB) or prolonged infusion (PI) against 7 gram-negative pathogens: *Klebsiella pneumoniae*, *K. oxytoca*, *Escherichia coli*, *Enterobacter cloacae*, *E. aerogenes*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. Unit-specific minimum inhibitory concentration (MIC) distribution data were generated using antibiogram data over a decade for 4 intensive care units within our institution: medical ICU, cardiovascular ICU, surgical ICU, and neurosurgical ICU. Published pharmacokinetic parameter estimates in critically ill patients, combined with this MIC distribution data, were utilized to perform Monte Carlo simulations for each antimicrobial regimen. The percentage of time for which the unbound concentration of antibiotic remained above the MIC ($fT > MIC$) was utilized as the pharmacodynamic target for each agent: 40% $fT > MIC$ for meropenem, 50% $fT > MIC$ for piperacillin/tazobactam, 60% $fT > MIC$ for aztreonam, and 70% $fT > MIC$ for cefepime. Regimens were modeled using Oracle Crystal Ball software to determine the likelihood of achieving >90% probability of target attainment (PTA). Because resistance rates were significantly higher for *P. aeruginosa* and *A. baumannii*, cumulative PTAs for *K. pneumoniae*, *K. oxytoca*, *E. coli*, *E. cloacae*, and *E. aerogenes* were analyzed separately to determine the relative PTA for Enterobacterales in each ICU. **Results:** No intermittent infusion regimens of piperacillin/tazobactam, aztreonam, or cefepime achieved >90% PTA for any organism. Piperacillin/tazobactam 4.5 g infused over 4 hours (PI q6h) and aztreonam 2 g PI q6h failed to achieve adequate PTA for Enterobacterales with only 84% and 85% PTA, respectively. For Enterobacterales, the only regimens to achieve >90% PTA

included cefepime 2 g infused over 3 hours (PI q8h) and meropenem 1g IB q8h with 95% and 99% PTA, respectively. Meropenem 2 g PI q8h was the only regimen capable of achieving >90% PTA for both *A. baumannii* and *P. aeruginosa* with 97% and 92% PTA, respectively. **Conclusions:** Although utilization of high doses and prolonged infusions dramatically improve the pharmacodynamics of β -lactam therapy, the only regimen capable of achieving adequate PTA for all organisms analyzed was meropenem 2g PI q8h. To reduce carbapenem use, combination therapy may be considered for critically ill patients receiving aztreonam, cefepime, or piperacillin/tazobactam for empiric treatment of gram-negative infections.

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Difference in Susceptibility Between Carbapenemase- and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae

Justin Clark and David Burgess

Background: Carbapenem-resistant Enterobacteriaceae (CRE) remain among the most urgent infectious threats according to the CDC Threats Reports. Although focus has often been placed on carbapenemase-producing phenotypes, there is increasing interest in distinguishing the optimal treatment and outcomes of carbapenemase-producing (CP) and non-carbapenemase-producing (NCP) CRE. We compare antimicrobial susceptibility patterns between CP-CRE and NCP-CRE isolated from patients at our academic medical center. **Methods:** All CRE isolates of *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella aerogenes*, *K. oxytoca*, and *K. pneumoniae* in adult inpatients from 2010 to 2019 were included in this study. Susceptibility testing was performed using the BD Phoenix Automated System (BD Diagnostics, Sparks, MD). CLSI susceptibility break points were utilized in the susceptibility analyses of all antimicrobials tested. To determine carbapenemase production, isolates resistant only to ertapenem were considered NCP-CRE, and those resistant to both ertapenem and meropenem were considered CP-CRE. Statistical comparisons of susceptibility profiles were performed using either the χ^2 test or the Fisher exact test. All data preprocessing and statistical analyses were performed using Python software. **Results:** Over the decade, we identified 291 CRE isolates (216 isolates resistant only to ertapenem and 75 resistant to ertapenem and meropenem). The ertapenem-resistant-only phenotype comprises ~66% of the total CRE population and is largely composed of *E. cloacae* (67%). As expected, most β -lactam susceptibilities were negligibly low between the 2 groups; however, other clinically relevant antimicrobials (aminoglycosides, fluoroquinolones, and sulfamethoxazole/trimethoprim) exhibited starkly different susceptibility profiles (*P* value **Conclusions:** These findings suggest that the most predominant CRE phenotype at our institution is not carbapenemase production. Evaluation of outcomes between CP- and NCP-CRE should be pursued further. The large differences in the MIC distributions may lead to differing outcomes for the affected patients.

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Stewardship Nightmare: Ceftolozane/Tazobactam-Resistant *Pseudomonas aeruginosa* Infections Accelerated by the COVID-19 Pandemic

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Background: The Centers for Disease Control and Prevention reported 32,600 cases, 2,700 deaths, and healthcare costs of 767 million dollars

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Table 1. Demographics and Clinical Characteristics

	Patients with CRPA (N=13)
Demographics	
Age (mean, range), years	62, 31-78
Female (n, %)	6 (46)
Risk factors	
Long-term care facility (n, %)	2 (15)
Hospitalization in prior 90 days (n, %)	6 (46)
IV antibiotics in prior 90 days (n, %)	5 (38)
ICU level care and intubation (n, %)	9 (69)
Renal failure (n, %)	10 (77)
Immunocompromised* (n, %)	3 (23)
Bone Marrow or Solid Organ Transplant	0 (0)
SARS-CoV-2 PCR positive on admission (n, %)	5 (38)
Infections from respiratory source (n, %)	9 (69)
Outcomes	
Length of stay post positive culture (median, IQ range), days	18 (7, 27)
Antibiotic days of therapy for CRPA (median, IQ range)	11 (9, 17)
Hospital Mortality (n, %)	8 (62)

* HIV/AIDS or Biologic/Steroids

attributed to multidrug-resistant *Pseudomonas aeruginosa*. A recent study of 128 patients with nosocomial pneumonia due to *P. aeruginosa* showed the noninferiority of ceftolozane-tazobactam compared to meropenem. However, the resistance of ceftolozane-tazobactam due to AmpC mutations has been described. Compared with 2019, we observed an increase from 2 to 13 cases of ceftolozane-tazobactam-resistant *P. aeruginosa* (CRPA) during the COVID-19 pandemic at our institution in the Bronx, New York. **Methods:** A report of patients with CRPA between March and August 2020 was obtained. Data collected included demographics, hospitalization/IV antibiotic use in prior 90 days, SARS-CoV-2 PCR result, ICU admission, length of stay, antibiotic days of therapy, mortality, etc. **Results:** In total, 13 patients with CRPA infection were reviewed (Table 1). Among them, 2 patients were on the same inpatient medical-surgical unit but separated by 5 months. Also, 11 patients were from different medical-surgical units or ICUs. In addition, 5 patients (38%) were SARS-CoV-2 PCR positive. None of these COVID-19 patients were cohorted on the same unit, making horizontal spread of CRPA or COVID-19 unlikely. Finally, 8 of these patients died while hospitalized (4 were COVID-19 patients). **Conclusions:** We found a high incidence of mortality in patients with CRPA infection. Many patients had prolonged hospital stay and required ICU admission. Few patients were from long-term care facilities. Given the associated morbidity and mortality, increased surveillance and intensified antimicrobial stewardship efforts are needed to mitigate the impact of CRPA during the COVID-19 pandemic.

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Treatment of Extensively Drug-Resistant (XDR) *Acinetobacter* in US Veterans' Affairs (VA) Medical Centers

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Background: Infections caused by *Acinetobacter* spp are often healthcare acquired and associated with high mortality. Extensively drug-resistant

(XDR) *Acinetobacter* are nonsusceptible to at least 1 agent in all but 2 or fewer antibiotic classes. Few of the new antibiotics targeting multi-drug-resistant gram-negative bacteria are effective against XDR *Acinetobacter*. Recent national guidelines for treatment of resistant gram-negative infections do not include *Acinetobacter*, leaving a knowledge gap in best practices. **Methods:** This retrospective cohort study included microbiology, clinical, and pharmacy data from all patients hospitalized between 2012 and 2018 at any Veterans' Affairs medical center who had cultures that grew XDR *Acinetobacter* spp. Bivariate unadjusted analyses compared clinical outcomes by monotherapy versus combination therapy. Using mixed-effects ordinal logistic regression, propensity score-adjusted models accounting for severity of illness and other variables associated with treatment were fit to compare outcomes. **Results:** Of 11,546 patients with 15,364 cultures that grew *Acinetobacter* spp, 408 patients (3.5%) had 666 cultures (4.3%) with XDR *Acinetobacter*. Moreover, 276 of these patients (67.6%) had gram-negative targeted antibiotic treatment within -2 to +5 days from the culture. Furthermore, 118 patients (42.8%) received monotherapy, most commonly piperacillin-tazobactam (n = 54, 45.7%) or an anti-*Pseudomonas* cephalosporin (n = 21, 17.8%). Also, 158 (57.2%) patients received combination therapy, most commonly a carbapenem (n = 93, 58.9%) and/or polymyxin (n = 68, 43.0%). Moreover, 41 patients (25.9%) received both a carbapenem and polymyxin. In both unadjusted and adjusted analyses, there were no significant differences in the odds of 30-day mortality (aOR, 1.43; 95% CI, 0.86-2.38) or 1-year mortality (aOR, 1.04; 95% CI, 0.68-1.60) between combination therapy and monotherapy groups. Among 264 patients (96%) whose cultures occurred during an inpatient or long-term care admission, unadjusted analyses showed increased odds of in-hospital mortality (OR, 1.89; 95% CI, 1.08-3.29) and longer postculture length of stay in the combination therapy group: median, 23 days (IQR, 11-57) versus 14 days (IQR, 7-32) (P = .02). However, with propensity score adjustment, these associations were no longer significant. Furthermore, there was no significant difference in odds of 90-day readmission between groups in either unadjusted or adjusted analyses (aOR, 1.20; 95% CI, 0.74-1.95). **Conclusions:** In this large national cohort of patients with XDR *Acinetobacter* cultures, more patients received combination therapy than monotherapy, and carbapenems and polymyxins were the most-used classes. However, there were no significant differences in outcomes between patients receiving combination therapy and monotherapy, suggesting lack of clinical benefit to the common practice of treating XDR *Acinetobacter* infections with multiple antibiotics. Further research is needed to determine optimal treatment strategies for this pathogen.

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Extended-Spectrum B-Lactamases in *E. coli* Isolates From Hospitalized Patients: A Single-Center Snapshot From Croatia

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Background: A significant increasing trend in the prevalence of *Escherichia coli* strains that produce extended-spectrum β -lactamases (ESBLs) has been observed in recent years, both in the community setting and in the healthcare arena. We aimed to provide a snapshot of the current situation with *E. coli* β -lactamase-producing strains in a single general hospital by appraising their β -lactamase content and plasmid types, which will inform further clinical and research efforts. **Methods:** Our study population consisted of all hospitalized patients in different clinical units of the General Hospital in Slavonski Brod during a 1-year period: internal medicine, infectious disease, surgery, urology and ICU. Phenotypic tests for the detection of ESBLs and plasmid-mediated AmpC β -lactamases were initially pursued, followed by the molecular detection (polymerase chain